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## Therapy of steroid-resistant inflammatory bowel disease

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**Abstract:** BACKGROUND AND AIMS: Although systemic corticosteroids are successfully administered for the induction of clinical response and remission in the majority of patients with inflammatory bowel disease (IBD) presenting with a flare, a proportion of these patients demonstrate a primary nonresponse to steroids or in the case of an initial response, they develop a resistance or a steroid dependence. Long-term therapy with corticosteroids for treatment of IBD should be avoided, given the high frequency of adverse treatment effects. Knowledge about treatment strategies in case of steroid nonresponse is therefore highly relevant. **METHODS:** A systematic literature research was performed using Medline and Embase to summarize the currently recommended treatment strategies for steroid-resistant IBD. **RESULTS:** Treatment of steroid-resistant Crohn's disease is based on the introduction of immunomodulators such as azathioprine, 6-mercaptopurine or methotrexate, the anti-TNF drugs infliximab, adalimumab and certolizumab pegol. In the case of steroid resistance in ulcerative colitis, aminosalicylates, the above-mentioned immunomodulators, infliximab, adalimumab or calcineurin inhibitors such as ciclosporin or tacrolimus may be administered. **CONCLUSION:** This review summarizes the current evidence for treating steroid-resistant IBD.

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# Therapy of Steroid-Resistant Inflammatory Bowel Disease

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## Key Words

Crohn's disease • Ulcerative colitis • Steroid-resistant inflammatory bowel disease

## Abstract

**Background and Aims:** Although systemic corticosteroids are successfully administered for the induction of clinical response and remission in the majority of patients with inflammatory bowel disease (IBD) presenting with a flare, a proportion of these patients demonstrate a primary nonresponse to steroids or in the case of an initial response, they develop a resistance or a steroid dependence. Long-term therapy with corticosteroids for treatment of IBD should be avoided, given the high frequency of adverse treatment effects. Knowledge about treatment strategies in case of steroid nonresponse is therefore highly relevant. **Methods:** A systematic literature research was performed using Medline and Embase to summarize the currently recommended treatment strategies for steroid-resistant IBD. **Results:** Treatment of steroid-resistant Crohn's disease is based on the introduction of immunomodulators such as azathioprine, 6-mercaptopurine or methotrexate, the anti-TNF drugs infliximab, adalimumab and certolizumab pegol. In the case of steroid resistance in ulcerative colitis, aminosaliclates, the above-mentioned immunomodulators, infliximab, adalimu-

mab or calcineurin inhibitors such as ciclosporin or tacrolimus may be administered. **Conclusion:** This review summarizes the current evidence for treating steroid-resistant IBD.

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## Introduction

Corticosteroids have been used since the 1950s in inflammatory bowel disease (IBD) and they remain one of the most effective treatments in a disease flare [1]. These drugs represent effective anti-inflammatory agents for inducing response and remission in IBD patients with moderate to severe disease activity. They act via inhibition of several inflammatory pathways such as the suppression of interleukin transcription, the induction of I $\kappa$ B that stabilizes the NF- $\kappa$ B complex, the suppression of arachidonic acid metabolism and the stimulation of lymphocyte apoptosis within the lamina propria of the gut [2].

Precise evidence on the most effective dose and duration of therapy is lacking. Sixty milligrams (mg) of prednisolone seems to not be more effective than 40 mg, but it is associated with a higher frequency of adverse events [3]. Guidelines suggest starting with an initial oral dose of 40–60 mg (0.75–1 mg/kg) prednisolone daily followed by a tapering [4, 5]. A commonly used regimen for steroid

tapering consists of reducing dosages above 30 mg daily in 10-mg steps per week and reducing dosages of 30 mg daily and below in 5-mg steps per week. Neither the long-term remission rates nor the duration of remission is influenced by the initial dose or the rate of steroid tapering [5, 6]. The goal of every IBD therapy is the achievement of a steroid-free remission. Steroids have no role as maintenance therapy in either Crohn's disease (CD) or ulcerative colitis (UC) [7].

About half the patients treated with steroids will suffer from side effects. Following the administration of supra-physiological doses of steroids, cosmetic problems (e.g. acne, moon-face and edema), diabetes, dyspepsia or sleep and mood disturbances may occur. Furthermore, patients on steroids are confronted with an increased risk for infections. Prolonged use of steroids has been associated with osteoporosis, osteonecrosis, myopathy and cataracts. In addition, children and adolescents may suffer from growth retardation. Typical steroid-withdrawal effects include adrenal insufficiency, the corticoid-withdrawal syndrome and raised intracranial pressure [2].

The natural history of first exposure to corticosteroids shows a 30-day outcome of complete remission in 48–58% of CD patients, a partial remission in 26–32% and no response in 16–20% [6, 8]. In UC, immediate outcomes were complete remission in 54%, partial remission in 30% and no response in 16% of the patients [8].

The phenomenon of steroid resistance is not confined to IBD, suggesting that it may be an inherent property of an individual which becomes important in the presence of inflammatory disease [1]. Several molecular mechanisms of glucocorticoid resistance have now been identified, including the activation of mitogen-activated protein kinase pathways by certain cytokines, the excessive activation of the transcription factor activator protein 1, reduced histone deacetylase-2 expression, raised macrophage migration inhibitory factor and increased P-glycoprotein-mediated drug efflux [9].

### **Definition of Steroid-Resistant and Steroid-Dependent Disease**

IBD patients who have still active disease, despite prednisolone or an equivalent of up to 0.75 mg/kg/day over a period of 4 weeks, are defined as having steroid-resistant or steroid-refractory disease. Patients who are either unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting without recurrent active disease, or who have a relapse

within 3 months of stopping steroids are considered as having steroid-dependent disease [10–13].

Steroid resistance, dependence or a primary nonresponse should prompt an escalation of medical treatment, alternatively, surgery should be considered.

### **Steroid Resistance in Crohn's Disease**

Before increasing or changing therapy in steroid-resistant CD, complications such as an abscess or infection must be ruled out by appropriate imaging techniques or stool analyses. Furthermore, surgery should also be considered as an option, especially in CD patients with severe ileocecal involvement. Different treatment strategies have been shown to be effective for steroid resistance; these will now be further discussed below.

#### *Purine Analogs*

Thiopurine drugs, represented by mercaptopurine (6-MP) and its prodrug azathioprine (AZA) have cytotoxic and immunosuppressive properties. The appropriate maintenance dose is 2–2.5 mg/kg/day of AZA and 1–1.5 mg/kg/day of 6-MP, respectively. They are widely used in steroid-refractory or steroid-dependent IBD patients. They have proven efficacy for the induction of remission in active CD and for maintaining remission and having steroid-sparing properties in quiescent steroid-dependent CD [14–17]. In the recent SONIC study, 30% of the 170 patients receiving AZA alone had a corticosteroid-free clinical remission after 6 months [18]. About 9% of IBD patients are resistant to thiopurines and between 15 and 28% experience adverse reactions [19].

#### *Methotrexate*

Methotrexate (MTX) 25 mg/week (oral, subcutaneous or intramuscular) may be used as an alternative to thiopurines. This is an established therapy for the induction and maintenance of remission in CD [20, 21]. Injections might be preferred due to unpredictable intestinal absorption via the oral route [22].

#### *Anti-TNF Therapies*

There are currently three biologic agents licenced for the treatment of CD in Switzerland: infliximab (Remicade®) and adalimumab (Humira®) are monoclonal IgG1 anti-TNF antibodies and certolizumab pegol (Cimzia®) is a pegylated anti-TNF Fab-antibody fragment. These three anti-TNF agents have proven efficacy in CD in various controlled trials. Most of these trials did not explic-

itly address steroid resistance but were used in patients with moderate to severe disease.

The European Crohn's and Colitis Organisation states in their consensus statement from 2010 that patients with evidence of active disease refractory to steroids should be treated with anti-TNF therapy, with or without thiopurines or MTX (EL1a, RG B for infliximab) [4]. They also state that all currently available anti-TNF therapies appear to have similar efficacy and adverse-event profiles, so the choice depends on availability, route of delivery, patient preference, cost and national guidelines [4].

### *Infliximab*

The randomized, double-blind SONIC study assessed the efficacy of infliximab with or without AZA in 508 adult patients with moderate to severe CD naïve to biologics and immunosuppressants. Remarkably, at baseline, only 27.4% of patients were on systemic corticosteroids. Patients were randomized to receive AZA monotherapy, infliximab monotherapy or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily. The primary end point of the study was corticosteroid-free clinical remission at week 26. Of the patients receiving combination therapy, at week 26, 56.8% were in corticosteroid-free clinical remission compared to 44.4% receiving infliximab only ( $p = 0.02$ ) and 30.0% receiving azathioprine only ( $p < 0.001$  for the comparison with combination therapy and  $p = 0.006$  for the comparison with infliximab). Similar numerical trends were found at week 50 [18].

The GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives) trial evaluated the usefulness of short-term infliximab combined with thiopurines in steroid-dependent CD patients. One hundred and thirteen steroid-dependent patients with active CD were stratified into 2 groups: AZA/6-MP failures and AZA/6-MP-naïve patients. Patients were randomized to infliximab 5 mg/kg or placebo at weeks 0, 2 and 6. All patients were treated with stable doses of AZA/6-MP throughout the 52-week trial. Their primary end point was clinical remission [Crohn's Disease Activity Index (CDAI)  $<150$ ] off steroids at week 24. Significantly more patients receiving infliximab plus AZA/6-MP compared with patients receiving AZA/6-MP alone were in steroid-free clinical remission at week 12 (75 vs. 38%;  $p < 0.001$ ) and week 24 (57 vs. 29%;  $p = 0.003$ ). They concluded that infliximab plus AZA/6-MP was more effective than AZA/6-MP alone in steroid-dependent CD patients [23].

### *Adalimumab*

In the CLASSIC-I trial, several dosage regimens were compared to placebo for the induction of remission in 299 anti-TNF-naïve patients with moderate to severe CD [24]. Patients were randomized to receive subcutaneous injections at weeks 0 and 2 with adalimumab 40/20 mg, 80/40 mg or 160/80 mg or placebo. In the placebo group ( $n = 74$ ), 34% ( $n = 25$ ) were on steroids and 30% on immunomodulators (AZA, 6-MP or MTX) compared to 32% on steroids and 29% on immunomodulators in the groups that were treated with adalimumab ( $n = 225$ ). The highest remission rate (defined as CDAI  $<150$  points at week 4) was observed with 36% ( $p = 0.001$ ) in the 160/80-mg group compared to 12% in the placebo group. The percentage of patients off steroids at week 4 was not assessed as an end point in this study [24]. In the CHARM trial (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance), patients received open-label induction therapy with adalimumab 80 mg (week 0) followed by 40 mg (week 2). At week 4, patients were stratified by response (a drop in CDAI of at least 70 points) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week (e.o.w.) or adalimumab 40 mg weekly up to week 56. [25] End points were the percentage of randomized responders achieving clinical remission at weeks 26 and 56. The percentage of randomized responders in remission was greater in the adalimumab 40-mg-e.o.w. and 40-mg-weekly groups compared to the placebo group at week 26 (40, 47 and 17%, respectively;  $p < 0.001$ ) and week 56 (36, 41 and 12%, respectively;  $p < 0.001$ ). Forty-four percent of patients were on steroids and 47% on immunomodulators (AZA, 6-MP or MTX). At week 26, out of the randomized responders, 3, 35 and 30% of patients treated with placebo, adalimumab 40 mg e.o.w. and adalimumab 40 mg weekly, respectively, achieved a corticosteroid-free remission ( $p < 0.001$  for each adalimumab group compared to placebo). At week 56, 6, 29 and 23% of patients treated with placebo, adalimumab 40 mg e.o.w. and adalimumab 40 mg weekly, respectively, achieved corticosteroid-free remission ( $p < 0.001$  for adalimumab 40 mg e.o.w. vs. placebo and  $p = 0.008$  for adalimumab 40 mg weekly vs. placebo).

### *Certulizumab Pegol*

In the PRECISE (Pegylated Antibody Fragment Evaluation in Crohn's Disease Safety and Efficacy) 2 trial, patients with moderate to severe CD received induction therapy with 400 mg certolizumab pegol s.c. at weeks 0, 2 and 4 [26]. Patients with a clinical response (CDAI reduction of at least 100 points from baseline) at week 6 were stratified according to their baseline C-reactive



protein level and randomly assigned to 400 mg of certolizumab pegol or placebo every 4 weeks up to week 24 with a follow-up till week 26. Sixty-four percent of patients (428 of 668) showed a response at week 6, the response was maintained till week 26 in 62 % of patients with a baseline CRP of at least 10 mg/l receiving certolizumab pegol compared to 34% in the placebo group ( $p < 0.001$ ). In the placebo group, 21% ( $n = 44$ ) of patients were on corticosteroids and 25% ( $n = 52$ ) on immunomodulators compared to 22% ( $n = 47$ ) on steroids and 27% ( $n = 59$ ) on immunomodulators in the certolizumab group. The percentage of steroid-free patients at week 26 was not reported in this trial. Neither the response rate nor the remission rate differed significantly between the 2 patient groups i.e. those who were and those who were not on concomitant steroids or immunomodulators, or both.

### Steroid Resistance in Ulcerative Colitis

Steroid-dependency in UC defines a patient, who fails to taper steroid doses below 10 mg within 16 weeks (starting dose 0.75–1 mg/kg oral prednisone-equivalent) or who relapses within 12 weeks after the discontinuation of steroid treatment. A patient not responding to 0.75–1 mg/kg of oral prednisone equivalent within 4 weeks is defined as having steroid-refractory or steroid-resistant UC [10, 27]. This classification is made after the exclusion of infection by appropriate stool tests and is best reassessed by sigmoidoscopy/colonoscopy with biopsies to confirm the diagnosis and/or to rule out complications like cytomegalovirus colitis or cancer. The universal goal, as in CD, is to withdraw steroids completely whenever possible.

Practical treatment algorithms for moderate to severe UC are provided in recent Swiss consensus recommendations [28].

In steroid-refractory UC in a patient in a clinically stable condition without the need for rapid induction, thiopurines (AZA 2–2.5 mg/kg or 6-MP 1–1.5 mg/kg) can be administered [29]. Unlike in CD, the efficacy of thiopurines in UC has been proven for maintenance therapy, but only as an alternative treatment [30]. It may be worth trying to optimize conventional treatment, especially to maximise the dose of 5-ASA treatment or to add topical 5-ASA [22].

If the patient is still clinically stable but not responding after 12–24 weeks, biological therapy must be considered.

The efficacy of infliximab in UC was demonstrated in 2 large clinical trials. In the ACT-1 and ACT-2 (Active

Ulcerative Colitis Trials 1 and 2) studies, patients with moderate to severely active UC received induction with infliximab at weeks 0, 2 and 6, followed by maintenance infusions every 8 weeks. Infliximab was superior to placebo for achieving clinical response, clinical remission, mucosal healing and reducing corticosteroid use up to weeks 30 (ACT-2) and 54 (ACT-1) [31].

The ACT-1 and ACT-2 extension studies could reveal that long-term treatment with infliximab was effective and well tolerated for up to 3 additional years [32]. In a retrospective multicenter study primary nonresponse to infliximab was noted in 22% of patients [33].

Recently, adalimumab was also shown to be more effective than placebo in inducing and maintaining clinical remission in patients with moderate to severe UC in a large trial with 494 patients [34]. The drug was administered subcutaneously: 160 mg at week 0, 80 mg at week 2 and then 40 mg e.o.w.

In the severely ill, hospitalized patient with the need for rapid induction, steroids are administered intravenously, such as 60 mg of methylprednisolone or 400 mg of hydrocortisone daily [29]. The overall response rate of steroids can be expected to be 67% [35]. A close teamwork between the gastroenterologist and the experienced colorectal surgeon is mandatory at this stage of the disease (at the latest), in order not to miss the best timing for colectomy.

In case of resistance to intravenous steroids, especially in the AZA-naïve patient, intravenous cyclosporine at a dose of 2mg/kg can be started [28]. If the patient is responding, AZA is added and oral cyclosporine is continued for at least 3 months as a bridging therapy [28].

If the severely ill patient had failed prior therapy with AZA/6-MP, due to the lack of a good exit strategy, infliximab at 5mg/kg at weeks 0, 2 6 and then every 8 weeks can be started [28].

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